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Bacterial home goal by harpins

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Host–pathogen interactions are dynamic and multifactorial; whether a microorganism succeeds or fails in colonizing a potential host depends on factors from both organisms. A successful pathogen has to overcome the defenses of the host. In bacteria that are pathogenic for animals or for plants, particularly Gram-negative organisms, a large number of genes are essential to infect host tissue and establish disease. Expression of these genes is generally controlled by environmental conditions such as temperature, pH, salt concentration and nutrient availability[1,2].

Pathogenicity, hypersensitive reaction and elicitors

In the Gram-negative plant pathogens *Erwinia*, *Pseudomonas* and *Xanthomonas*, genes organized in clusters of 25–40 kb are fundamentally involved in any obvious interaction with a plant (for a review see Ref. 3). These genes have been designated *hrp* (hypersensitive reaction and pathogenicity) because they are essential not only for pathogenicity towards a susceptible host plant, but also for interaction with resistant host varieties and with plants that are not a host for that pathogen. In plants, the hypersensitive reaction (HR) (Ref. 4) is a rapid defense reaction involving localized plant cell death and production of substances such as phenolics and phytoalexins at the site of infection. The HR prevents pathogen spread and thus halts disease development.

In the wild, plants are resistant to the majority of pathogens. The HR, therefore, is an important defense mechanism against all kinds of possible disease agents (bacteria, fungi, nematodes and viruses). It is not only important to interactions of pathogens with nonhost plants, but also to interactions between plants that carry resistance genes and microorganisms that are pathogens for that species.

Although the genes involved in plant defense[5,6] are becoming better understood, very little is known about the nature of the initial signals and their perception. Induction of the HR in a bacterium–plant interaction requires functional *hrp* genes and appears to be mediated by signal molecules or 'elicitors'. Recent DNA sequence analyses indicate that several putative Hrp proteins from different species are related and may be involved in a secretion system reminiscent of secretion of Yops (*Yersinia* outer proteins) in *Yersinia*[7–11]. So far, only one specific elicitor of the HR in a bacterium–plant interaction has been described. The *avrD* gene from *Pseudomonas syringae* pv. *tomato* mediates production of a low-molecular-mass compound that specifically induces the HR only in the soybean plant (a nonhost) when it carries the corresponding *Rpg4* resistance gene[5,12].

Harpins

Recently, two bacterial HR-inducing proteins, called 'harpins', were identified in *Erwinia amylovora*[13] and *P. syringae* pv. *syringae*[14]. Although the harpins differ in primary sequence, they have several features in common: they are glycine rich and heat stable, and they both induce an HR in tobacco, a nonhost plant for these bacteria. The genes encoding harpins are localized within the *hrp* clusters and obviously have a dual role in that they are also required for pathogenicity towards the normal host plant. Both *hrp* clusters allow nonpathogenic bacteria, such as *Escherichia coli*, to induce an HR in tobacco after recombinant expression, suggesting that the genes for the tobacco HR elicitors are present within the clusters[15,16].

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The first harpin to be identified, harpin$_{Ea}$, is a cell-envelope-associated protein encoded by the *hrpN* gene of *Er. amylovora*, a pathogen of pear and apple[13]. Recently, He and co-workers[14] have used an elegant approach to identify harpin$_{Pss}$, which is encoded by the *hrpZ* gene in the bean pathogen *P. s.* pv. *syringae*. Lysates of an expression library in *E. coli*, made using the cloned *P. s.* pv. *syringae hrp* cluster, were directly screened for HR-inducing activity on tobacco leaves. Two proteins were identified, one of which was an amino-terminal deletion of harpin$_{Pss}$ with even higher activity than the full-size protein; whether processing occurs during natural infection is not clear. Interestingly, the carboxyl terminus contains two short, direct repeats that are essential for elicitor activity. The activity is in the same range as that of the *Erwinia* harpin$_{Ea}$; however, to elicit an HR in other plants requires higher levels of the elicitor. He *et al.* show convincingly that the secretion of harpin$_{Pss}$ by *P. s.* pv. *syringae* depends on a product called HrpH that is closely related to proteins in other plant pathogens, and also in animal pathogens such as *Yersinia* and *Shigella*, where they are essential for protein secretion[9,10,14].

These exciting findings help verify the model that Hrp proteins are involved in the transport of elicitors and virulence factors[7]. Not surprisingly, the results presented by He and co-workers[14] also stimulate many questions. It needs to be shown that harpin$_{Pss}$ is actually secreted when the bacterium interacts with tobacco tissue (the *hrp* genes were induced *in vitro*). The concentration needed for HR induction (more than 600 nM) is much higher than one would expect for specific signal molecules. Are harpins toxins? Most importantly, what is their function in pathogenicity, and why do they

not elicit an HR in the host plant? Are harpins the only elicitors of nonhost HR in tobacco and possibly in other plants? Is the same mechanism used in tobacco to recognize both the *Erwinia* and the *P. s.* pv. *syringae* harpins? Is host resistance different in mechanism from nonhost resistance? Answers to this fascinating puzzle require the identification of more HR elicitors and their putative plant receptors.

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Initiation and spread of α-herpesvirus infections

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Herpesviruses are large animal viruses with a DNA genome varying from approximately 120 to 250 kb. Based on their biological properties, the Herpesviridae have been divided into three subfamilies, the α-, β- and γ-herpesvirinae, prototypes of which are the human pathogens herpes simplex virus (HSV), cytomegalovirus (HCMV) and Epstein–Barr virus (EBV), respectively. As enveloped viruses, they depend on two consecutive processes for infectious entry into target cells: (1) attachment of free virions to cells and (2) penetration, that is, fusion of virion envelope and cellular cytoplasmic membrane leading to release of the nucleocapsid into the cell. Virion envelope glycoproteins play important roles in both these processes (see Refs 1,2 for recent reviews).

After infection of primary target cells, virus spread can occur by several different mechanisms. Infected cells may release infectious virions that reinitiate infection from outside. In addition, direct viral cell-to-cell spread from primary infected cells to adjacent noninfected cells may occur. In the host, virus may be disseminated by circulating infected cells that adhere to noninfected tissues and transmit infectivity directly. Recent results on HSV and pseudorabies virus (PrV) shed more light on these processes in α-herpesviruses. PrV causes Aujeszky's disease in swine, which is characterized by nervous and respiratory symptoms, and reproductive failure. Unlike HSV, PrV is not pathogenic for humans. However, the two viruses have several features in common, including a broad host range *in vitro*, and several species besides the natural host can be infected experimentally. In addition, all of the known PrV glycoproteins are related to homologous glycoproteins in HSV (Ref. 1)*.

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Attachment

Binding of free infectious virus to target cells involves interactions between virion envelope glycoproteins and cellular virus receptors. Herpes virions contain a large number of different virus-encoded envelope glycoproteins that might participate in attachment. A well-known example of a cellular herpesvirus receptor is the B-cell membrane protein CR2 (CD21), which binds EBV (Ref. 3). Recent studies have demonstrated that several α- (reviewed in Ref. 1), β- and γ-herpesviruses[4,5] bind to their target cells by interaction of virion components with cell-surface glycosaminoglycans, principally heparan sulfate (HS)[6].

*At the 18th International Herpesvirus Workshop, a common nomenclature for α-herpesvirus glycoproteins was agreed on, based on designations of HSV glycoproteins. This nomenclature is used here.